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Avraham Ben-Nun
Itzhack Mendel
Ronit Bakimer
Masha Fridkis-Hareli
Dvora Teitelbaum
Ruth Arnon
Michael Sela
Nicole Kerlero de Rosbo

The autoimmune reactivity to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis is potentially pathogenic: effect of copolymer 1 on MOG-induced disease

Abstract Multiple sclerosis (MS), an autoimmune disease of the central nervous system (CNS) characterized by primary demyelination, is believed to result from an autoimmune attack against myelin components. In view of their ability to induce experimental autoimmune encephalomyelitis (EAE), an animal model for MS, the quantitatively major myelin proteins – myelin basic protein (MBP) and proteolipid protein (PLP) – have been extensively studied as the relevant primary antigens in MS, and therapeutic approaches have been targeted to counteract autoimmune reactivity to MBP and PLP. Accordingly, copolymer 1, a random synthetic amino acid copolymer cross-reactive with MBP and highly protective against the induction of EAE with MBP or PLP, is now being extensively tested in clinical studies as a therapeutic agent for MS. However, increasing evidence suggests that autoimmune reactivity against other CNS-specific myelin proteins could also be involved in the pathogenesis of MS. In this context, we have demonstrated that peripheral blood lymphocytes from patients with MS respond predominantly to myelin oligodendrocyte glycoprotein (MOG) rather than to MBP or PLP, suggesting an important role for cell reactivity against MOG in the pathogenesis of MS. We have demonstrated that T-cell reactivity to MOG can also be pathogenic by inducing neurological disease in H-2^u and H-2^b mice with the same peptide of MOG, pMOG 35–55. Most interestingly, the expression of the disease differed with the different MHC backgrounds. Induction of a differentially expressed disease in different strains of mice with the same myelin antigen makes this new model particularly relevant to MS, where different expression of the disease is seen in different patients. Therefore, notwithstanding the importance of the autoimmune reactivity to MBP and PLP in MS, the potentially pathogenic autoimmune reactivity to MOG must now also be taken into consideration in therapeutic approaches to MS. In this context, we have investigated the possible effect of copolymer 1 treatment on autoimmune reactivity to MOG and on the development of EAE induced by MOG. Copolymer 1 was found to inhibit the binding of MOG peptides to MHC molecules, as well as the proliferation of MOG-reactive T cells, in a dose-dependent manner. In parallel, injection of copolymer 1 concomitantly with the encephalitogenic MOG peptide exerted a strong protective effect against the development of EAE. These preliminary data on the effect of copolymer 1 on the autoimmune response to MOG in mice indicate that copolymer 1 may also be effective in cases of MS where the autoimmune response to MOG prevails, and should therefore be further investigated in this context.

Key words Multiple sclerosis · Experimental allergic encephalomyelitis · Encephalitogenic basic proteins · Copolymer 1

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A. Ben-Nun (✉) · I. Mendel
R. Bakimer · N. Kerlero de Rosbo
Department of Cell Biology,
Weizmann Institute of Science,
PO Box 26, Rehovot 76100, Israel

M. Fridkis-Hareli · D. Teitelbaum
R. Arnon · M. Sela
Department of Chemical Immunology,
Weizmann Institute of Science,
Rehovot, Israel

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by primary demyelination with axon sparing, which manifests itself clinically by moderate or severe neurological impairment depending on the form or stage of the disease. Accumulation of activated T lymphocytes in early MS lesions or plaques, as well as at the periplaque area and in surrounding normal-appearing white matter, strongly indicates that immunological mechanisms are involved in the pathogenesis of MS. In view of the restricted localization of MS lesions to the white matter, it is generally accepted that MS is a result of an autoimmune attack against myelin components. However, despite intensive efforts by many laboratories, the primary target antigen in MS has not yet been clearly identified. On the basis of their relative abundance, localization, and encephalitogenic activity, various myelin components have been investigated as possible target antigens (Table 1). Myelin basic protein (MBP) and proteolipid protein (PLP), the most abundant proteins of CNS myelin (30% and 50% of myelin proteins respectively), were found to be powerfully encephalitogenic, and MBP- and PLP-specific T cells are sufficient to cause experimental autoimmune encephalomyelitis (EAE), a well-accepted animal model for MS. Accordingly, MBP and PLP have been extensively studied as possible primary target antigens in MS.

EAE induced with MBP or PLP can be blocked by copolymer 1, a random synthetic amino acid copolymer composed of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. The highly protective effect of copolymer 1 against MBP- or PLP-induced EAE has led to clinical trials of copolymer 1 as a therapeutic agent for MS. However, although T-cell responses to MBP and PLP are likely to be of importance in the course of MS, evidence for their sine qua non participation in the pathogenesis of the disease is still lacking, and autoimmune responses to other myelin antigens may also play a major role in the initiation or progression of MS. In this context, increasing evidence suggests that myelin oligodendrocyte glycoprotein (MOG), a quantitatively minor CNS myelin antigen located at the surface of the outermost myelin lamella, is a relevant target antigen in MS. Consequently, notwithstanding the importance of the autoimmune reactivity to MBP and PLP in the pathogenesis of MS, autoimmune reactivity to MOG must now also be taken into consideration in therapeutic approaches to MS.

This article summarizes our studies on the autoimmune reactivity to MOG in MS and the encephalitogenic activity of MOG; these studies suggest that autoimmune recognition of MOG may play an important role in the pathogenesis of MS. This article also presents our preliminary data on the efficacy of copolymer 1 in blocking MOG-induced disease.

Relevant biochemical features of MOG

MOG has been identified as the antigen recognized by the monoclonal antibody 8–18C5 induced by rat cerebellar glycoprotein preparation [23]. MOG was demonstrated by immunohistochemistry to be located on oligodendrocyte surfaces and in the outermost lamellae of myelin sheaths [6, 21, 24]. It appears to be a specific antigen of the CNS, as no reaction of anti-MOG antibodies with peripheral nerve has been detected [21, 23], and the expression of MOG mRNA was recently shown to be restricted to CNS tissue [9, 27]. Analysis of its sequence indicates that MOG is a member of the immunoglobulin superfamily, albeit an unusual member in that it has two transmembrane domains [9, 27], a feature at least partly responsible for its highly hydrophobic character. MOG seems to be present in all mammalian species examined so far [5, 21, 23, 24] but is apparently not expressed in non-mammalian vertebrates [5]. MOG is present in very small amounts in CNS myelin, representing about 0.01–0.05% of myelin proteins [2]. The function of MOG is unclear. However, because of its localization on the surface of the myelin sheath [6], together with the fact that it is a late marker of oligodendrocyte maturation [34] and that its expression coincides with late stages of myelination [21, 23, 27], its role has been postulated to be that of a signal to arrest further myelination [5, 9] and maintain myelin integrity [27]. We have further speculated that, in view of its exclusive

Table 1 Possible target antigens in multiple sclerosis (*MS*)

Antigen	CNS	PNS	Location	Percent in CNS myelin	EAE	Demyelinating antibodies	T-cell reactivity in MS
MBP	+	+	Myelin	~30%	+	–	+
PLP	+	+	Myelin	~50%	+	–	+
MOG	+	–	Myelin	0.01–0.05%	+	+++	+
MAG	+	+	Myelin	~1%	–	±	±
S100β	+	+	Astrocytes, Schwann and Muller cells		±	?	?
GalC	+	+	Myelin	20–25%	± (?)	++	?

expression in the CNS, MOG (a member of the immunoglobulin superfamily [9, 27]) may play a role in the adhesion between neighboring myelinated fibers that, in the CNS, are not isolated from each other by a basal lamina as in the peripheral nervous system (PNS) but appear in close contact with each other; MOG could therefore be involved in the maintenance of axon bundles in the CNS [7]. As a consequence, autoimmune recognition of MOG could be a major determinant in autoimmune CNS disease, resulting in destabilization of white matter structure.

Antibodies to MOG have demyelinating activity

In vivo studies

In acute EAE produced in Lewis rats by injection of purified MBP or by passive transfer of monospecific MBP-reactive T cells, there is little or no demyelination despite widespread inflammation [29]. However, extensive CNS demyelination can be induced in these animals by intravenous injection of purified monoclonal anti-MOG antibodies, at the time when the blood-brain barrier is breached [28, 32]. Intravenous injection of the anti-MOG antibody alone in control animals had no effect, nor did injection of normal mouse IgG in EAE animals. In other forms of EAE, similar treatments with anti-MOG antibody lead to increased severity of the disease and augmentation of demyelination [18, 24]. Further evidence that the presence of anti-MOG antibody within the CNS causes demyelination comes from experiments where intrathecal injection of 8–18C5 in normal rats induced demyelinating lesions on the surface of the spinal cord [17]. In addition, the possible involvement of MOG as a target antigen in demyelinating diseases is shown by the presence of anti-MOG antibodies in guinea pigs with chronic relapsing EAE [22] and the occurrence of cross-reactive idiotypes on these specific autoantibodies [11]. Most importantly, in chronic relapsing EAE, serum demyelinating activity (assayed in vivo by intrathecal injection of normal rats) correlates with anti-MOG antibody titer [22]. In addition, the aforementioned studies suggest that although MOG is present in low amounts in myelin [2, 23], it must have a high immunogenic potential, since immunization with whole CNS tissue homogenate generates detectable levels of anti-MOG antibodies [22].

In vitro studies

Although antibodies directed against the major myelin proteins, MBP and PLP, are present in demyelinating EAE sera, polyclonal antibodies raised against the isolated proteins MBP, PLP, and myelin-associated glycoprotein (MAG) do not demyelinate CNS tissue cultures [10]. While antibodies directed against myelin glycolipids do initiate demyelination in CNS cultures [29], the presence in EAE sera of detectable anti-glycolipid antibodies is not a prerequisite for demyelination in vitro [20] or in vivo [33]. This indicates that antibodies directed against other myelin antigens must also be involved in the demyelination process [33]. In this context, it is noteworthy that EAE sera devoid of reactivity against MBP, PLP, and cerebrosides but containing antibodies against the CNS myelin glycoprotein M2 have been shown to demyelinate CNS cultures [19, 20]. Indeed, on the basis of immunological cross-reactivity, tissue and cellular localization, and molecular weight, M2 previously described by Lebar et al. [19, 21] has now been identified as MOG [10, 21]. The idea that in vitro demyelination by EAE sera may be attributed to anti-MOG antibody activity is strongly supported by the specific dose-related demyelinating effect of purified monoclonal anti-MOG antibody in fetal rat brain aggregating cell cultures [13].

In MS, anti-MOG antibodies and secreting B cells have been reported in blood and cerebrospinal fluid [36, 39]. Although MS immunoglobulins can induce myelinolysis [12], the specificity of the demyelinating antibody has not been determined.

Analysis of the T-cell response to myelin antigens in MS: predominance of autoimmune reactivity to MOG

In view of the encephalitogenic activity of purified MBP and PLP and, more specifically, because MBP- or PLP-specific T cells are sufficient to cause EAE [4, 16, 26, 31, 38], these two most abundant myelin proteins have been regarded as prime candidate antigens to elicit relevant immune responses in MS, and T-cell reactivity to these myelin antigens in MS has been extensively investigated. However, controversial results indicate that, although specific responses to these antigens are likely to be of importance in the course of the disease, they may not represent the primary response involved in the pathogenesis [30]. It has recently been acknowledged that autoimmune recognition of quantitatively minor myelin autoantigens in MS could also play a major role in disease initiation or progression. Because of their low abundance, these antigens are difficult to obtain in a highly purified form and in sufficient quantities; hence the paucity of reports investigating T-cell reactivity to quantitatively minor myelin components. MOG, a highly hydrophobic molecule present in very small quantities in CNS tissue [2, 9], is extremely difficult and cumbersome to purify in the quantity and quality required to analyze specific T-cell reactivity by standard assays. However, in one study where problems associated with purification of MOG were circumvented by using an immunospot assay to detect interferon γ secretion by antigen-specific lymphocytes, MOG-reactive T cells were observed in peripheral blood of most of the 14 patients studied, whereas only 25% of the 28 controls

Table 2 Reactivity to myelin antigens by peripheral blood lymphocytes (PBLs) from MS patients: predominant response to MOG (+ 2 < SI < 3, ++ 3 < SI < 5, +++ 5 < SI < 10, ++++ SI > 10; *RR* relapsing-remitting, *CP* chronic progressive). Adapted from Kerlero de Rosbo et al. [14], by copyright permission of The American Society for Clinical Investigation

Patient no.	Sex, age	Diagnosis	Type	Proliferative response of PBLs to			
				MOG	MBP	MAG	PLP
MS1	F, 43	Definite	RR	++	–	–	–
MS2	F, 33	Definite	RR	++	+	–	–
MS3	F, 41	Probable	?	–	–	–	–
MS4	F, 48	Definite	CP	++++	–	–	–
MS5	F, 55	Probable	RR	–	–	–	–
MS6	F, 66	Definite	RR	+++	++	–	+
MS7	F, 46	Definite	RR	–	–	–	–
MS8	F, 46	Definite	RR	–	–	–	–
MS9	F, 40	Definite	RR	+	–	–	–
MS10	M, 44	Definite	RR	–	+	–	–
MS11	F, 17	Definite	RR	+	+	–	++
MS12	M, 55	Definite	CP	–	–	–	–
MS13	F, 42	Definite	RR	–	–	–	–
MS14	F, 40	Definite	RR	++	–	–	–
MS15	F, 46	Definite	RR	–	–	–	–
MS16	F. 51	Definite	RR	–	–	–	–
MS17	F. 42	Definite	RR	–	–	–	–
MS18	F, 36	Definite	RR	+	–	–	–
MS19	M, 33	Definite	RR	+++	–	–	–
MS20	F, 43	Definite	RR	+++	–	–	–
MS21	M, 52	Definite	RR	–	–	–	–
MS22	M, 47	Definite	RR	–	–	–	–
MS23	M, 56	Definite	CP	++	–	–	–
MS24	F. 50	Probable	RR	+++	++	ND	–

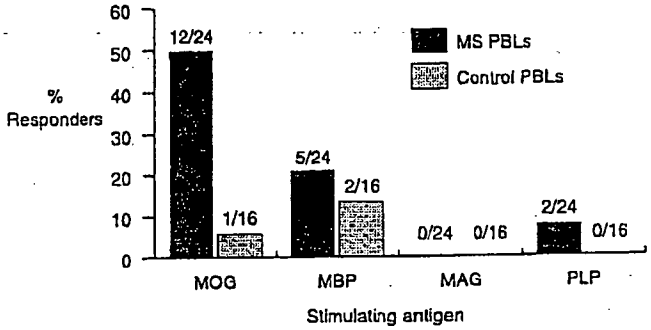
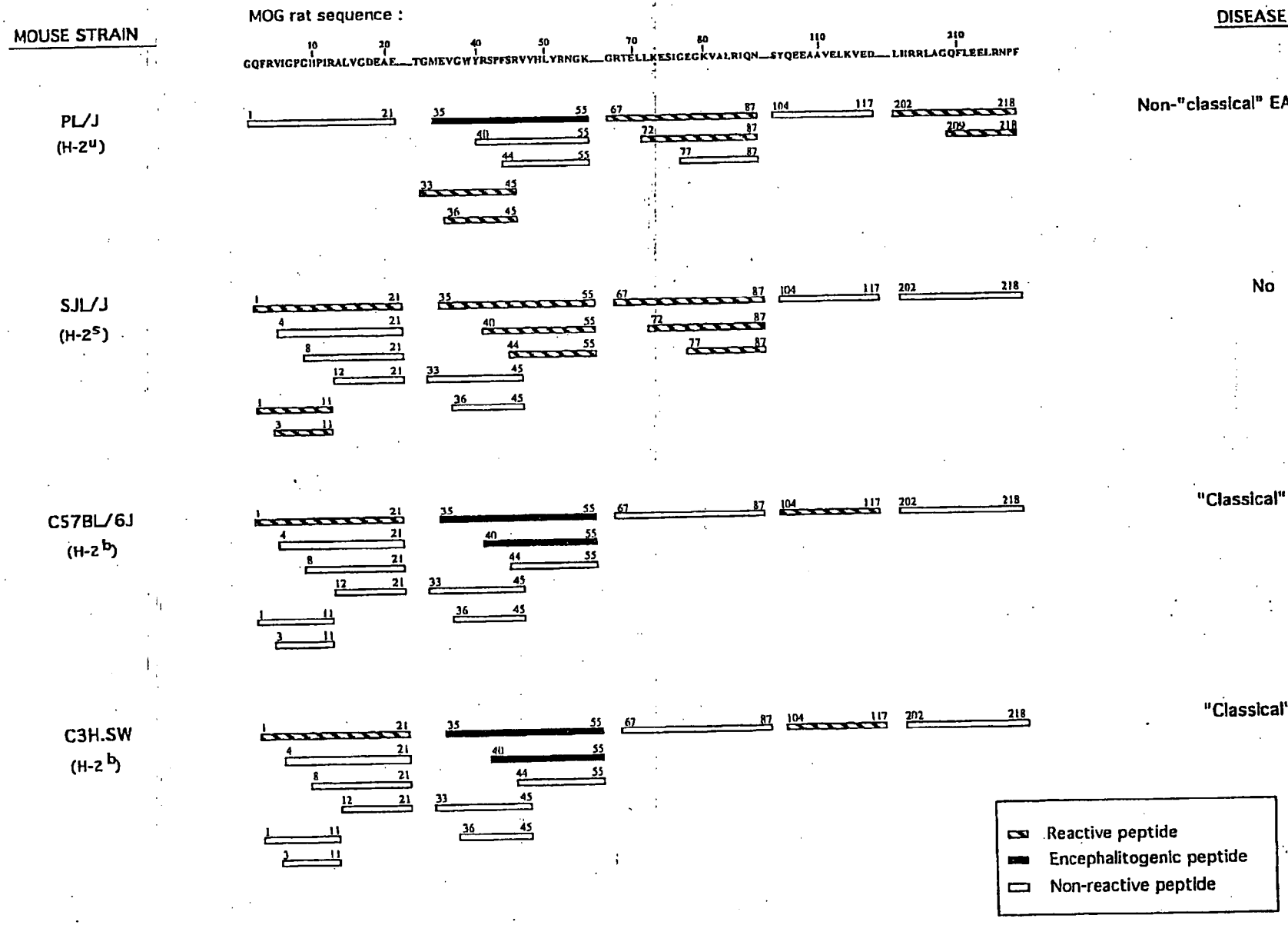


Fig. 1 Summary of responses to myelin antigens by multiple sclerosis (*MS*) and control peripheral blood lymphocytes (*PBLs*) [14]

showed reactivity [36]. We have been successful in purifying MOG to homogeneity [1] in amounts sufficient to investigate the T-cell proliferation to MOG in MS [14]. Thus, the proliferative response to highly purified human MOG by peripheral blood lymphocytes (PBLs) of patients with MS was investigated in the context of reactivity to other highly purified myelin antigens such as MBP, PLP, and MAG [14]. The greatest incidence of proliferative response by MS PBLs was to MOG, as 12 out of the 24 patients tested reacted, and of these, 8 reacted exclusively to MOG (Table 2). In contrast, only one control individual out of 16 tested reacted to MOG. The incidence of responses by PBLs of MS patients to MBP, PLP, and MAG was low, as 5, 2, and 0 patients, respectively, reacted to these antigens; the frequency of these responses did not differ greatly between MS patients and controls (Fig. 1). These data, which indicate that T-cell reactivity to MOG is predominant in MS, strongly suggest that cell-mediated immune response to this antigen plays an important role in the pathogenesis of this autoimmune disease. However, the encephalitogenic activity of MOG must be unequivocally demonstrated before assigning a pathogenic role to autoimmune reactivity to MOG.

Encephalitogenic activity of MOG: different expression of disease in mice with different MHC backgrounds

To ascertain whether the T-cell reactivity to MOG that we observed in MS patients [14] is potentially pathogenic and estimate the extent to which autoreactivity to MOG may play a role in the pathogenesis of MS, we investigated the potential encephalitogenic activity of MOG in mice [15, 25]. In view of the inherent difficulties encountered in purifying MOG, MOG peptides (pMOG) predicted to represent potential T-cell epitopes were synthesized and tested for their ability to induce T-cell response and neurological disease in mice. Figure 2 summarizes our preliminary results on the T-cell response to these peptides, with some delineation of the epitopes recognized as well as the encephalitogenic activity of the peptides. All strains of mice

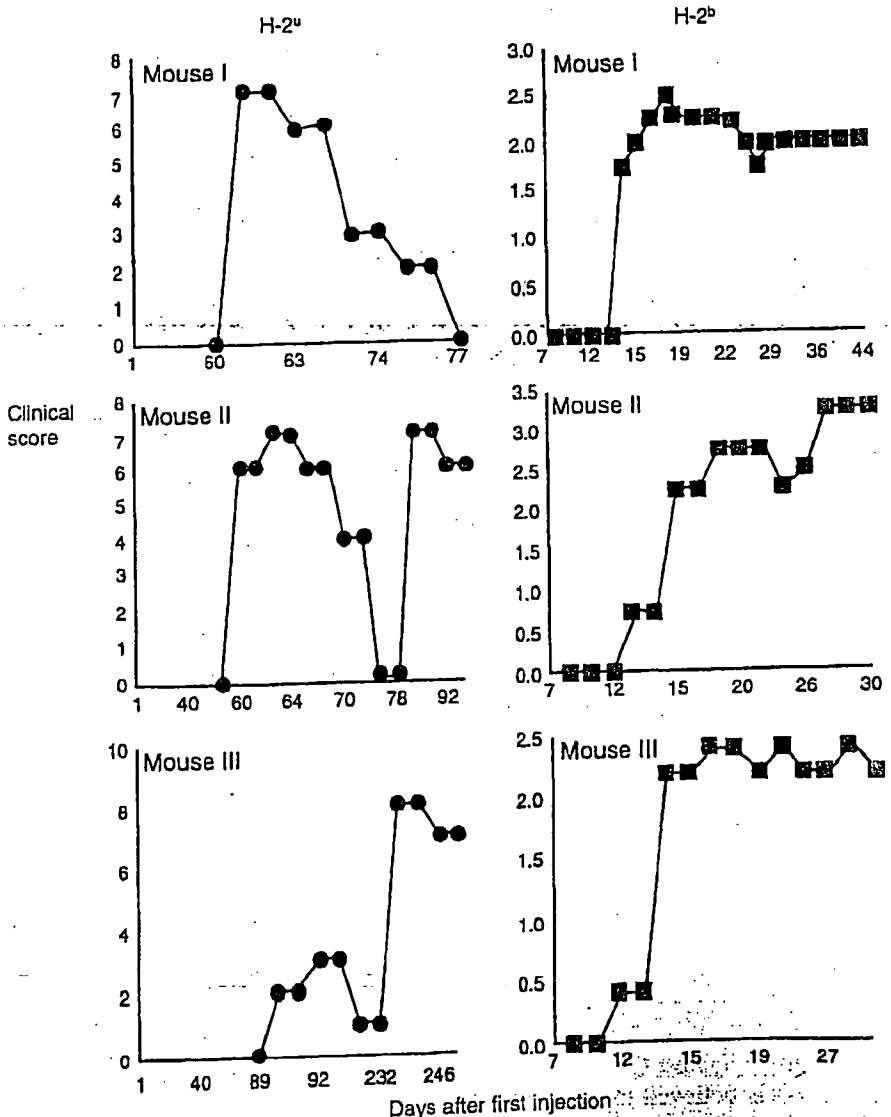

MOG rat sequence :
GQFRVIGPGHPIRALVGDEAE TGMEVGWYRSPFSRVVHLYRNGK GRTELLKESIGEGKVALRIQN STQEEAAVELKVED LHRRLAGQFLEELRNPF
MOUSE STRAIN
DISEASE
PL/J
(H-2u)
Non-"classical" EAE, MS-like
SJL/J
(H-2s)
No
C57BL/6J
(H-2b)
"Classical" EAE
C3H.SW
(H-2b)
"Classical" EAE
Reactive peptide
Encephalitogenic peptide
Non-reactive peptide

so far tested – PL/J (H-2^u), SJL/J (H-2^s), C57BL/6J (H-2^b), and C3H.SW (H-2^b) – were able to mount a T-cell response to at least some of the five MOG peptides synthesized. T-cell lines that could be raised to the same peptide in strains of different MHC backgrounds appeared to differ in their epitope definition, e.g., the epitope for pMOG 35–55-reactive T cells from PL/J mice could be located to the N-terminal pMOG 36–45, while pMOG 35–55 T cells selected from SJL/J mice recognized an epitope within the C-terminal pMOG 44–55 [15]. In mice of the same MHC background, however, T-cell lines could be raised to the same peptides and apparently recognized the same epitope; e.g., pMOG 40–55 is recognized by pMOG 35–55-specific T cells from C57BL/6J and C3H.SW (H-2^b) mice [25].

As can be seen in Fig. 2, one peptide, pMOG 35–55, appears to be strongly immunogenic, as it induced a primary T-cell response from which a line could be raised in all strains tested [15, 25]. Most importantly, pMOG 35–55 was the only MOG peptide that could induce a neurological disease. Of the mice from the five strains tested – SJL/J (H-2^s), PL/J (H-2^u), B10.PL (H-2^u), C57BL/6J (H-2^b), and C3H.SW (H-2^b) – SJL/J mice were the only ones that did not develop a neurological disease following immunization with pMOG 35–55. It should be noted, however, that SJL/J mice develop "classical" EAE upon injection with pMOG 92–106 [3]. In H-2^b mice, the disease presented as chronic, classical EAE with caudo-rostral ascending paralysis and neuropathology comparable with that observed in EAE induced with MBP or PLP, except that the disease was consistently non-remitting [25]. These features differ markedly from those of the disease induced with pMOG 35–55 in PL/J mice, where the delayed onset and atypical expression and progression of the clinical signs are more reminiscent of MS [15]. Hence, in different mouse strains, the same MOG peptide can induce typical EAE characterized by ascending paralysis or

◀ **Fig. 2** Scheme summarizing the T-cell reactivity to MOG peptides representing predicted T-cell epitopes, in mice with different MHC backgrounds [15, 25]. Adapted in part from Kerlero de Rosbo et al. [15]

Fig. 3 Clinical expression of MOG-induced disease in H-2^u and H-2^b mice [15, 25]. The clinical signs for MOG-induced disease in H-2^u mice are scored on a different scale in view of the atypical clinical expression of the disease in these mice [15]. Adapted in part from Kerlero de Rosbo et al. [15] ▶



atypical EAE with unpredictable clinical signs (Fig. 3). pMOG 35–55-reactive T cells from H-2^b and H-2^u mice were sufficient to induce severe clinical and pathological disease upon transfer into their respective naive syngeneic recipients ([25]; unpublished data). Rather interestingly, passive transfer of pMOG 35–55 T cells also resulted in a different clinical expression, as observed with the disease induced by the peptide ([25]; unpublished data).

As shown in Fig. 2, attempts were made to delineate, within pMOG 35–55, the minimal epitope encephalitogenic for H-2^b and H-2^u mice. Although further studies are required to define precisely the borders of these epitopes, the minimal epitopes responsible for induction of disease in H-2^b and H-2^u mice are obviously different. Thus, pMOG 35–55-reactive T cells selected from C57BL/6J mice reacted with pMOG 40–55 but not with pMOG 36–45, and pMOG 40–55 was strongly encephalitogenic in these mice [25]. Conversely, pMOG 35–55-reactive T cells selected from PL/J mice did not react with pMOG 40–55 but recognized pMOG 36–45 [15]. Accordingly, pMOG 40–55 did not induce disease in PL/J mice [15], and pMOG 36–45 did not induce disease in H-2^b mice [25]. Thus, with pMOG 35–55 as the encephalitogen, the epitope recognized may determine the development of a differently expressed disease in these mouse strains with different MHC backgrounds. These data, which demonstrate unequivocally the encephalitogenic activity of MOG, support our contention that MOG is an encephalitogenic protein, similar to MBP and PLP, and that autoimmune reactivity to MOG may play an important role in autoimmune CNS disease pathogenesis. In addition, the two types of disease induced in different mouse strains with the same MOG peptide may be particularly useful as models for MS. Such differential expression of MOG-induced disease is likely to be most relevant to MS research and therapy, in view of the possible parallel with the clinical expression of MS, where neurological impairment can vary significantly from patient to patient. The unpredictable clinical features of the disease induced by MOG in PL/J mice resemble those of MS more than those of classical EAE, suggesting that MOG-induced disease may prove to be a fairly good animal model for MS. On the other hand, the unremitting clinical course of chronic EAE induced by MOG in H-2^b mice will provide an excellent, reliable model to investigate therapeutic approaches to MS.

Effect of copolymer 1 on autoimmune reactivity to MOG

Clinical trials of the effectiveness of copolymer 1 as a therapeutic agent for MS are being conducted at several centers. The incentive to treat MS with copolymer 1 has come primarily from the demonstration of its highly protective effect against EAE induced by MBP [35, 37]. This protection is believed to occur via "suppressive cross-reactivity" with MBP. Recently, copolymer 1 was also shown to effectively block EAE induced by PLP (unpublished data). As mentioned above, we have demonstrated that the reactivity to MOG in MS may predominate over the reactivity to MBP, PLP, or MAG [14]. Our data on MOG-induced disease in mice provide indisputable evidence that T-cell reactivity to MOG can be pathogenic and may thereby play a major role in the pathogenesis of MS. Accordingly, autoimmune reactivity to MOG must now be taken into consideration in therapeutic approaches to MS. It is therefore of major importance, in view of the imminent recognition of copolymer 1 as a treatment for MS, to investigate and monitor the effect of copolymer 1 on T-cell reactivity to MOG and on MOG-induced disease in order to predict better the efficacy of copolymer 1 in the therapy of MS, particularly in cases where reactivity to MOG prevails. We have obtained preliminary results indicating that the effect of copolymer 1 on autoimmune reactivity to MOG is similar to its effect on autoimmune reactivity to MBP or PLP. The immunological mechanisms involved in the inhibition are still unclear.

Copolymer 1 inhibits in vitro T-cell response to MOG

The in vitro effect of copolymer 1 on the proliferative response to MOG was tested using highly specific, MOG-reactive T-cell lines. As can be seen in Fig. 4, copolymer 1 inhibited the proliferation of MOG-reactive T cells in a dose-dependent manner, which is similar to what has been observed for the in vitro proliferative T-cell response to MBP and PLP. In the attempt to understand the possible mechanism of the inhibitory action of copolymer 1, its

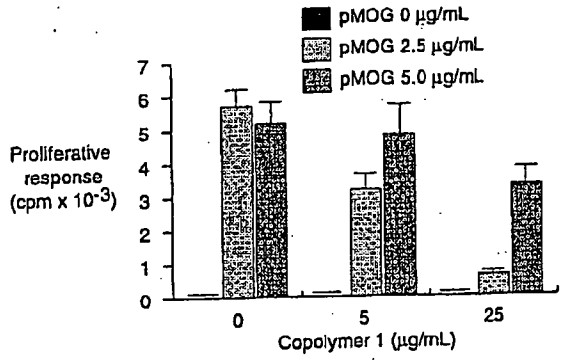


Fig. 4 Copolymer 1 inhibits in vitro T-cell response to MOG. pMOG 67–87-reactive T cells raised in SJL/J mice were cultured in the presence of pMOG 67–87 (2.5 and 5.0 µg/ml) as described previously [15], in the presence or absence of copolymer 1 (5.0 and 25.0 µg/ml). [^{3}H] Thymidine (1 µCi/well) was added for the last 16 h of the incubation and the cultures were harvested and counted using a Matrix 96 Direct beta-counter (Packard Instr., Meriden, Conn.). The proliferative response is measured as the [^{3}H] thymidine incorporation expressed as mean counts per minute (cpm) of triplicate cultures. Similar results were obtained with pMOG 35–55 specific T cells

Table 3 Copolymer 1 (Cop 1) inhibits binding of MOG peptide to MHC class II. Analysis of the binding of biotinylated pMOG to MHC class II molecules and inhibition of binding by copolymer 1 and anti-MHC antibodies were performed as described previously [8], using splenic macrophages isolated from C57BL/6J (H-2^b) mice

pMOG	% Binding in the presence of				% Binding inhibition by		
	None	Cop 1	anti-I-A^b	anti-I-A^s	Cop 1	anti-I-A^b	anti-I-A^s
35–55	63	26	26	60	59	59	4
40–56	55	20	22	56	63	60	0
44–56	23	12	12	25	48	48	0

effect on the binding of MOG peptide to MHC was assessed. Table 3 shows that copolymer 1 competes with MOG peptides for binding to MHC class II molecules to the same extent as the specific anti-MHC class II antibodies.

Effect of copolymer 1 on MOG-induced disease

The protocol followed in a pilot study to investigate the effect of copolymer 1 on MOG-induced EAE in H-2^b mice was the same as that used to demonstrate inhibition of MBP-induced EAE. Thus, copolymer 1 was injected concomitantly with the encephalitogenic MOG peptide emulsified in complete Freund's adjuvant. The preliminary data suggest that copolymer 1 may also exert an inhibitory effect on the development of MOG-induced EAE in H-2^b mice. The onset of the disease was generally retarded, with significantly milder clinical manifestations as compared with the control group injected with pMOG 35–55 only. In addition, 3 of the 10 mice treated with copolymer 1 were fully protected against disease induction. Interestingly, D-Cop 1, a control copolymer composed of the same four amino acids as copolymer 1 but in the D-configuration, had a rather enhancing effect on the disease. Further studies with various protocols are needed to define the conditions required to fully inhibit the disease.

Conclusion

Several observations strongly suggest that autoimmunity to MOG plays an important role in MS and must be taken into consideration in therapeutic approaches. First, T-cell response to MOG in MS can predominate over that to other myelin proteins – MBP, PLP, and MAG. Second, the strong encephalitogenic activity of MOG in mice unequivocally demonstrates that autoimmune reactivity against MOG in MS is potentially pathogenic. Third, the differential expression of MOG-induced disease in mice with different MHC backgrounds may reflect differences in expression of MS in different patients. Fourth, in contrast to the other encephalitogenic proteins (MBP and PLP), MOG is apparently CNS-specific, a fact particularly pertinent to MS, which is strictly a CNS disease. MOG therefore appears to be a highly relevant target antigen in MS. Accordingly, immune-specific approaches to MS therapy should take autoreactivity to MOG into consideration. Our preliminary data, which seem to indicate that copolymer 1 inhibits MOG-induced disease in mice, strongly suggest that copolymer 1 should be investigated further in terms of its effect on the autoimmune response to MOG.

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